IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Docket No.: FUERTES-LOPEZ

In re PATENT Application of:	
LAURA FUERTES-LOPEZ & MARCOS TIMÓN-JIMENEZ	**Examiner: Anne Maria Sabrina Wehbe**
Appl. No.: 10/816,591	**Group Art Unit: 1633**
Filed: April 1, 2004	**Confirmation No.: 8510**
For: DNA EXPRESSION CONSTRUCT FOR THE TREATMENT OF INFECTIONS WITH LEISHMANIASIS	

REPLY BRIEF PURSUANT TO 37 C.F.R. §41.41

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(Signature) Aug. 10, 2010 (Date of Signature)

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S I R:

This reply brief is being filed pursuant to 37 C.F.R. §41.41 in response to the Examiner's Answer, mailed June 10, 2010.

REMARKS

In the Examiner's Answer, the Examiner made several statements in particular under the heading "(10) Response to Argument" that appellant wishes to address.

Issue 1

In her Answer, the Examiner questions applicant's argument that Gurunathan suggests that immunostimulatory bacterial sequences present in the plasmid encoding LACK contribute to the generation of IL-12 and IFN- and that therefore the skilled artisan would not have been motivated to use the MIDGE vector which lacks the majority of these sequences to express p36 LACK.

To support her position, the Examiner states (page 8, Ex. Answer, 3rd para.) that based on Figure 5 of Gurunathan et al. "the skilled artisan reading Gurunathan et al., could only conclude that the LACK DNA itself contributes to the generation of IFN-γ and results in the generation of a therapeutic immune response in vaccinated mice challenged with L. major." With this the Examiner is trying to establish that a skilled artisan would not regard the plasmid sequences that are nonessential for expression in the Gurunathan reference as beneficial for the immune response and therefore would not be discouraged from removing these sequences to arrive at the claimed invention.

The Examiner's conclusion is not correct. The reason is that based on the manner the Gurunathan experiment that is the basis for Figure 5 was carried out, there is an alternative explanation for the lack of IFN-γ expression in cells derived from mice that were only treated with control DNA. For this experiment mice were first immunized with either LACK DNA or control DNA, then infected with L. major. After infection, lymph node cells from these mice were harvested and exposed *in vitro* to LACK protein. During vaccination, cells that take up the LACK DNA construct and express and present LACK protein cause the activation and expansion of LACK specific CD8+ cells. Since these cells are LACK specific they will respond to a challenge by LACK protein with production of IFN-γ.

In the case of mice vaccinated only with control DNA, no activation and expansion of LACK specific CD8+ cells is expected for the fact that there was simply no LACK

expression in these cells to begin with and therefore no population of LACK specific CD8+ cells to respond to a challenge with LACK protein.

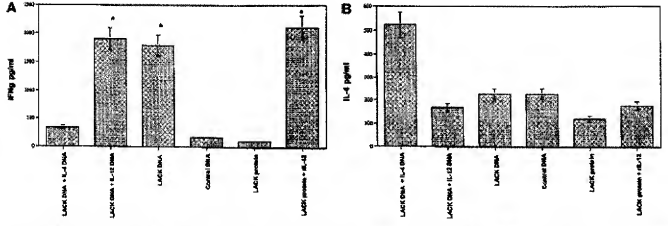


Figure 5. In vitro production of IL-4 and IFN-γ from lymph node cells of vaccinated mice infected with *L. major* at 6 wk after infection. Individual mice ($n = 3$) were euthanized and the draining lymph nodes were harvested 6 wk after infection. Single cell preparations were plated in triplicate in 96-well microtiter plates at 3×10^5 cells/200 μl in media alone or with LACK protein (10 μg/ml). 48 h later, supernatants were harvested and IFN-γ and IL-4 content were assayed by ELISA. Production of IFN-γ in media alone was <30 pg/ml. Production of IL-4 in media alone was usually 125 pg/ml or less. Data as shown represents the amount of IL-4 and IFN-γ averaged from three individual mice ± SEM. *P <0.005 in comparing IFN-γ produced from mice vaccinated with LACK DNA or LACK protein plus rIL-12 versus that produced from mice vaccinated with control DNA or LACK protein alone.

Thus, the interpretation by the Examiner in her Answer expands the scope of the Gurunathan specification beyond what is in fact described.

Issue 2

The Examiner's position that Gurunathan is the closest prior art but that Gurunathan does not have to provide motivation to combine with Wittig since Wittig provides the motivation, confirms the "template" approach by the Examiner.

The Examiner acknowledges that Gurunathan differs from the invention as claimed in that the DNA construct is a plasmid and not a MIDGE and further that the DNA is not covalently linked to the oligopeptide PKKKRKV. So, the Examiner continues to say that Wittig supplements Gurunathan by teaching a Midge vector (or dumbbell shaped expression construct) and an NLS. That the NLS is not identical to that as claimed seems to not matter since another reference discloses the PKKKRKV albeit in no context that would matter here.

Clearly, the Examiner uses as a starting point a reference cited as the closest prior art; only, it does not provide any motivation to go in the direction of the claim. By

taking the Wittig and the Makkerh filling in the gaps of Gurunathan is nothing short of the hindsight approach already argued by appellant. Gurunathan itself does not provide the skilled artisan with the direction in which to go. The Examiner insists when citing Gurunathan no motivation is necessary, even though the Examiner cites the reference as *the closest prior art*. Only if you are looking at Wittig does the skilled artisan get the idea of a useful vector. As the Gurunathan approach is flawed as already as carefully outlined under issue 1 it further contradicts the Examiner exposition.

Issue 3

In her Answer, the Examiner questions the veracity of appellant's data as set forth in the Figures of the application by stating that the administration of protein antigen generates different immune responses that the administration of nucleic acid encoding an antigen.

Appellant's results clearly demonstrate that LACK antigen (administered as protein or expressed from a plasmid) only generates immune response in the presence of either bacterial vector DNA, or rIL-12. This result is reproduced in other experiments shown in Figure 2, Figure 5A, Figure 6B and Figure 7. In each of these experiments the LACK antigen, when administered as protein alone, provides a very similar result to the empty vector. It is the combination of LACK DNA with bacterial vector sequence which stimulates the immune response.

The Examiner submits that failure of LACK protein to generate IFN γ production as opposed to LACK DNA is not indicative of the role of immunostimulatory sequences on the LACK DNA plasmid.

The Examiner points to the fact that protein antigens do not have access to the same antigen presentation pathways as antigens encoded on DNA vectors as in the case of the LACK DNA. The Examiner's argument therefore is that since LACK antigen encoded on the LACK DNA has access to MHC class I presentation to CD8+ cells, IFN-γ production is not the result of immunostimulatory sequences on the plasmid DNA but rather the result of stimulation of CD8+ cells through MHC class I presentation of expressed LACK antigen.

Applicant respectfully disagrees. First, it is noted that it was equally well known at the time of filing that unmethylated bacterial sequences have immunostimulatory effects whether or not they encode an antigen. Further, while it is true that Gurunathan shows that CD8+ might contribute to IFN-γ production, importantly, Gurunathan also demonstrates the essential contribution of CD4+ cells to IFN-γ production (Gurunathan et al., p. 1145). Stimulation of CD4+ cells results from antigen presentation via the MHC class II pathway. Both LACK DNA and LACK protein have access to the same MHC class II pathway. However, only LACK DNA contributes essentially to IFN-γ production but not LACK protein. It is therefore maintained that Gurunathan demonstrates the importance of immunostimulatory sequences to elicit effective immune responses.

Issue 4

In her Answer, the Examiner again questions the declaration of Dr. Timon-Jimenez.

a) The declaration clearly points out that it is known that the EDYP extension does not have a functional significance which is supported by the attached reference Lopez-Fuertes. The Examiner wants to have it both ways. In the case of the Wittig reference the relevant sequence is *inherently* included in the SV40 sequence even though the claimed NLS sequence is not specifically disclosed in Wittig. In the declaration however, the Examiner debates that the nonfunctional EDPYC has allegedly not been shown to be nonfunctional. Based on such a double standard, it is not justified to negate the declaration.

b) As to the reference attached to the declaration, the reference of the publication in "Vaccine" was supplied at the time the declaration was filed on April 1, 2009.

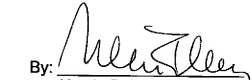
c) As to the scope of the claim, the claim requires a PKKKRKV sequence. A nonfunctional additional portion of EDPYC therefore does not change the scope of the claim.

Conclusion

Appellant submits that the Examiner in his attempt to present a prima facie case of obviousness failed to properly interpret the Gurunathan disclosure and to fully appreciate appellant's invention. With respect to the combination of Gurunathan and Wittig, as suggested by the Examiner, appellant again notes that the Examiner's Answer conjectures to explain the science of Gurunathan, how the Gurunathan plasmid can be modified by the Wittig MIDGE and the Makkerh sequence and completely ignoring the results as set forth in appellant's application and using the claimed invention as an instruction manual or "template".

For the foregoing reasons and the reasons stated in Appellant's Brief of Appeal, it is respectfully requested to overrule the Examiner's rejections.

Respectfully submitted,

By: 

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